1301254

PATENT SPECIFICATION

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NO DRAWINGS

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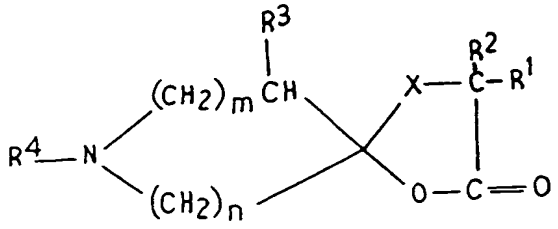
(54) SPIRO HETEROCYCLIC KETONE COMPOUNDS

(71) We, YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., a Japanese Company, of No. 35, Hirano-Machi 3-Chome, Higashi-Ku, Osaka, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

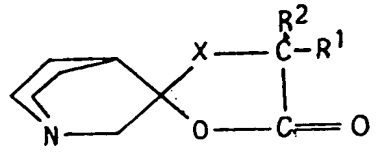
This invention relates to novel and therapeutically valuable spiro compounds.

According to the invention, there is provided a compound of the general formula:



(I)

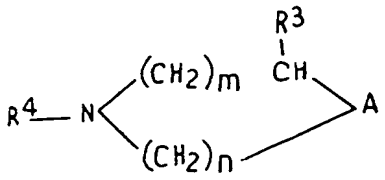
or a pharmaceutically acceptable acid-addition or quaternary ammonium salt thereof. In the above formula, each of R^1 and R^2 are the same or different and are H, CH_3, C_2H_5, phenyl, *p*-chlorophenyl or benzyl; X is O or S; R^3 is H and R^4 is H, alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, propyl, butyl), methoxycarbonyl, ethoxycarbonyl, acetyl, benzoyl, benzyl, phenethyl, pyridylmethyl (e.g. 2-pyridylmethyl, 3-pyridylmethyl), pyridylethyl (e.g. 2-pyridylethyl, 4-pyridylethyl), furfuryl, thenyl (e.g. 2-thenyl, 3-thenyl), cinnamyl, cinnamoyl, allyl or propargyl, and m plus n is 2 or 3 (m being 0 or 1 and n being 2 or 3); or R^3 and R^4 together represent $—CH_2—CH_2—$, in which case m is 2 and n is 1. In this latter csae the compounds of formula (I) are quinuclidine spiro compounds which can be represented by the formula



(II)

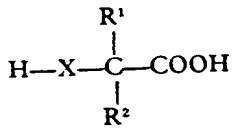
The compounds of formula (1) can be produced by the following methods:

(i) By the reaction of a compound of the formula



(III)

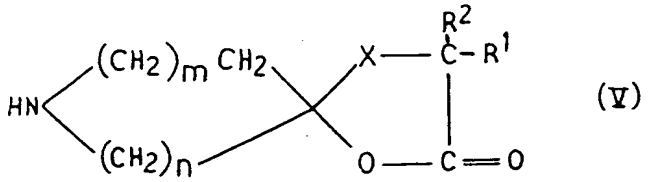
wherein A is —CO— or —$C(OH)_2$—, with a compound of the formula



(IV)

This reaction is usually carried out (a) in a solvent such as benzene, toluene, xylene, chloroform, dichloroethane, carbon tetrachloride, methanol, ethanol, 2-propanol or dioxane, in the presence of an acid catalyst such as *p*-toluenesulphonic, benzenesulphonic, sulphuric, phosphoric or hydrochloric acid, under reflux for 5 to 20 hours, while water produced is removed from the reaction system, or (b) in a solvent such as methanol, ethanol, 2-propanol, dioxane, chloroform, tetrahydrofuran, benzene, toluene or xylene, in the presence of a dehydrating agent such as calcium oxide, anhydrous magnesium sulphate, anhydrous zinc chloride, molecular sieve or N,N'-dicyclohexylcarbodiimide, at room temperature or an elevated temperature, for example at the boiling point of a solvent employed, for 3 to 20 hours.

(ii) By the reaction of a compound of the formula



(V)

with a compound of the formula

$$R^4—Y \qquad \text{(VI)}$$

wherein Y is halogen or a reactive radical such as methylsulphonyloxy, phenylsulphonyloxy or *p*-tolylsulphonyloxy.

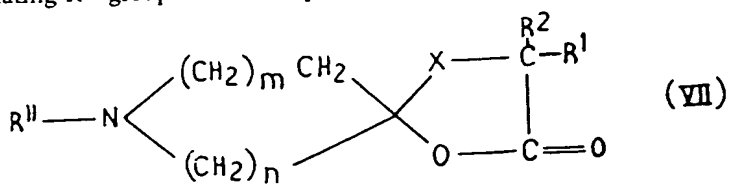
This reaction is carried out in a solvent such as methanol, ethanol, 2-propanol, benzene, toluene, xylene, chloroform, dimethylformamide, dioxane, tetrahydrofuran, acetone, methyl ethyl ketone or methyl acetate, in the presence of a deacidifying agent such as alkali metal carbonate, alkali metal hydrogen carbonate, alkali metal hydroxide, alkali metal alkoxide, trimethylamine, N,N-diethylaniline or pyridine, under reflux for 3 to 20 hours.

(iii) The compounds of formula (I) wherein R^4 is C_{1-4} alkyl may be produced by alkylating a compound of formula (V) with formaldehyde (for methylation) or dialkyl sulphate such as dimethyl sulphate, diethyl sulphate or dibutyl sulphate.

The methylation with formaldehyde is carried out be heating the mixture of a compound of formula (V) and formaldehyde and, if desired, in the presence of formic acid under reflux for 1 to 5 hours.

The alkylation with dialkyl sulphate is carried out in a solvent such as ether (e.g. ethyl ether, propyl ether, butyl ether), chloroform or benzene, in the presence of a deacidifying agent such as alkali metal carbonate, alkali metal hydrogen carbonate, alkali metal hydroxide or alkali metal alkoxide for several to 10 hours.

(iv) The compounds of formula (I) wherein R^4 is hydrogen atom may be produced by eliminating R'' group from a compound of the formula



(VII)

wherein R'' is benzyl or C_{1-2} alkoxycarbonyl.

The benzyl elimination is carried out by subjecting a compound (VII) (R'' being benzyl) to catalytic reduction using a catalyst such as palladium-carbon, palladium oxide or Raney-nickel, in an inert solvent such as water, methanol, ethanol, 2-propanol, glacial acetic acid or dioxane, under normal or increased pressure at room temperature or at an elevated temperature e.g. up to 100°C for 1 to 20 hours.

The alkoxycarbonyl elimination is carried out by treating a compound (VII) (R'' being C_{1-2} alkoxycarbonyl) with an acid such as hydrogen chloride, hydrogen bromide, hydrogen fluoride or perchloric acid in a solvent, preferably with 10—25% hydrogen bromide in acetic acid, under anhydrous conditions to avoid the decomposition of the spiro ring, or with an alkali such as sodium hydroxide, potassium hydroxide, barium hydroxide, calcium hydroxide or magnesium hydroxide in a solvent such as water, methanol, ethanol, 2-propanol, ethylene glycol or trimethylene glycol at about boiling point of the solvent employed for 2 to 25 hours.

The compounds of formula (I) can be converted into acid addition salts with various inorganic acids (e.g. hydrochloric, hydrobromic, nitric, sulphuric acid) or various organic acids (e.g. oxalic, maleic, fumaric, tartaric acid), and also into quaternary ammonium salts with methyl chloride, methyl bromide, methyl iodide, butyl iodide, methyl hydrogensulphate or dimethyl sulphate.

The compounds of formula (I) as well as their pharmaceutically acceptable acid addition and quaternary ammonium salts have acetylchloline antagonistic activity and gastric juice secretion inhibiting activity, and are useful as drugs for the treatment of various gastro-enteric spasms (algospasms), gastric hyperacidities and gastro-enteric ulcers.

For example, the compounds of formula (I) listed below (A, B, ... F) have the pharmacological properties illustrated by the tests given below.

A: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5] - decane methoiodide

B: 8 - butyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5] - decane methoiodide

C: 8 - methyl - 3 - methyl - 3 - phenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro-[4.5]decane methoiodide

D: 8 - methyl - 3 - benzyl - 3 - phenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro-[4.5]decane methoiodide

E: 8 - (2 - thenyl) - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro-[4.5]decane methoiodide

F: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1 - oxa - 4 - thia - 8 - azaspiro-[4.5]decane hydrochloride

G: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1 - oxa - 4 - thia - 8 - azaspiro-[4.5]decane methoiodide

H: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5]-decane ethobromide

J: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5]-decane methyl hydrogensulphate

K: 8 - methyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5]decane dimethyl sulphate.

L: 8 - cinnamyl - 3,3 - diphenyl - 2 - oxo - 1,4 - dioxa - 8 - azaspiro[4.5]decane methoiodide

M: 1 - azabicyclo[2.2.2.]octane - 3 - spiro2' - (5',5' - diphenyl - 1',3' - dioxolan - 4' - one) methoiodide

N: 1 - azabicyclo[2.2.2.]octane - 3 - spiro - 2' - (5',5' - diphenyl - 1',3' - dioxolan - 4' - one maleate

Tests were carried out using the following procedures:

(*A*) *Acetylcholine Antagonistic Activity*

Acetylchloline antagonistic activity was tested according to the method described by J.M. Van Rossum et al. in "Archives Internationales de Pharmacodynamie et de Therapie", Vol. 143, pages 240—246 and 299—330 (1963). pA_2 is the negative of the logarithm, to the base 10, of the molar concentration of the test compound which reduced the effect of a double dose of acetylcholine on contracting action of the guinea pig intestine compared with that of a single dose.

The results are shown in Table 1.

TABLE 1

Test Compound	Acetylcholine Antagonistic Activity, pA_2
A	9.3
B	7.0
C	6.6
D	7.8
E	7.3
F	7.2
G	8.2
H	8.8
J	9.4
K	9.3
M	8.6
N	8.5
Atropine (for comparison)	9.2
Scopolamine-N-butyl bromide (for comparison)	7.1

(*B*) *Effect on Gastric Juice Secretion in Shay Rats*

Effect on gastric juice secretion was tested according to the method described by Paul Bass and Margaret A. Patterson in "The Journal of Pharmacology and Experimental Therapeutics", vol. 156, pages 142—149 (1967). Wistar strain female rats (130—200 g.) were deprived of food for 48 hours and the pylorus was ligated. ED_{50} shows the subcutaneous dose of the test compound required for 50% depression of gastric juice secretion against the control Shay rats.

The results are shown in Table 2.

TABLE 2

Test Compound	Depressive Effect on Gastric Juice Secretion in Shay Rats, ED_{30} (mg./kg.)
A	0.06
B	2.8
C	6.4
D	1.0
E	3.3
G	1.5
H	0.05
J	0.04
L	2.0
M	0.2
N	1.2
Atropine	0.2
Scopolamine-N-butyl bromide	1.4

The compounds (I) and pharmaceutically acceptable acid addition and quaternary ammonium salts thereof can be admixtured safely per se or in the form of a pharmaceutical composition in admixture with a suitable carrier or adjuvant without causing harm to the patient.

The pharmaceutical composition can take the form of tablets, injectable solution, granules or powder. The following are examples of the compositions of the invention which may be administered for pharmaceutical purposes.

The invention thus also embraces a pharmaceutical composition containing a compound (I) or salt thereof as aforesaid in the form of an injectable solution in a physiologically acceptable liquid, or in the form of a composition for oral or parenteral administration together with a physiologically acceptable carrier or diluent.

(1) *Injectable solution contianing 1 mg. of compound J per ml. is prepared from the following composition*:

Compound J	:	1 mg.
Sodium Chloride	:	9 mg.
Water for Injection	:	A sufficient amount to make 1 ml.

(2) *0.5 mg. tablets are prepared from the following composition*:

Compound J	0.5 mg.
Lactose and Starch	70.5 mg.
Microcrystalline Cellulose	5.0 mg.
Methyl Cellulose	1.0 mg.
Magnesium Stearate	1.0 mg.
Talc	2.0 mg.
Total	80.0 mg./tablet

The pharmaceutical compositions may be administered orally or parenterally, usual daily doses lying in the range of 1.5 to 6.0 mg. per human adult.

The invention is illustrated by the following Examples in which "g.", "ml.", "m.p." and "b.p." represent "gram (s)", "milliliter(s)", "melting point" and "boiling point", respectively.

Example 1

A mixture of 17.1 g. of 1-ethoxycarbonyl-4-oxopiperidine, 11 g. of thioglycollic acid and 0.3 g. of *p*-toluenesulphonic acid in 200 ml. of benzene is heated under reflux with stirring in a flask provided with a water trap for 8 hours. After cooling, the reaction mixture is washed with water, with sodium bicarbonate solution and again with water. The mixture is dried over anhydrous sodum sulphate, and the residue is distilled off under reduced pressure. The residue is distilled under vacuum to give 17 g. of 8-ethoxycarbonyl-2-oxo-1-oxa-4-thia-8-azaspiro[4.5]decane as pale yellow liquid boiling at 177—179°C/0.2 mmHg and showing $n_D^{25.5}=1.520$. The liquid product solidifies on standing. The solid melts at 42—45°C.

Example 2

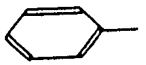
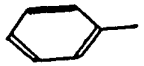
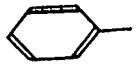
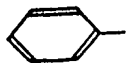
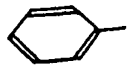
A mixture of 18.9 g. of 1-benzyl-4-oxopiperidine, 15.2 g. of DL-mandelic acid and 8 ml. of concentrated sulphuric acid in 400ml. of chloroform is heated under reflux with stirring in a flask with a water trap attached for 9 hours. After cooling, a viscous oil layer separates. The viscous oil is collected by decantation, and alkalified with an aqueous potassium carbonate solution. The crystals formed are collected by filtration, washed with water and recrystallized from 2-propanol to give 20 g. of 8-benzyl-2-oxo-3-phenyl-1,4-dioxa-8-azaspiro[4.5]decane as white crystals melting at 127°C. Its hydrochloride melts at 226°C.

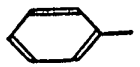
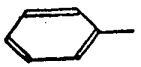
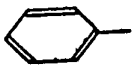
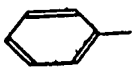
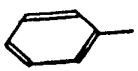
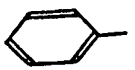
Example 3

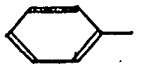
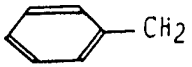
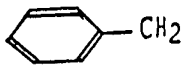
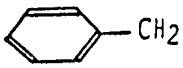
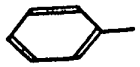
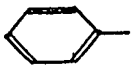
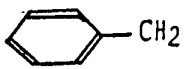
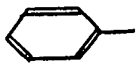
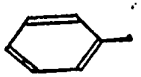
A mixture of 4.7 g. of 4,4-dihydroxypiperidine hydrochloride, 4.7 g. of 2-mercaptopropionic acid and 2 to 3 drops of concentrated sulphuric acid in 80 ml. of chloroform is heated under reflux in a flask with a water trap attached for 8 hours. After cooling. the crystals formed are collected by filtration and recrystallized from methanol to give 2.3 g. of 3-methyl-2-oxo-1-oxa-4-thia-8-azaspiro[4.5]decane hydrochloride as white crystals melting at 228°C.

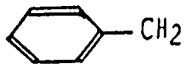
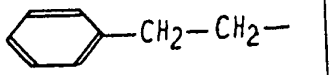
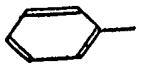
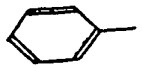
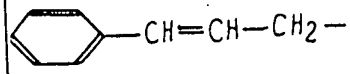
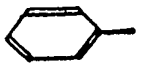
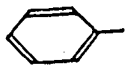
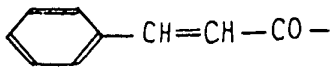
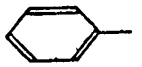
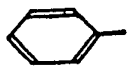
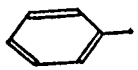
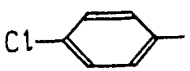
Examples 4 to 51

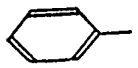
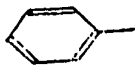
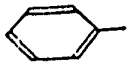
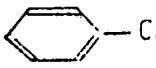
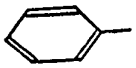
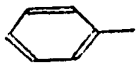
Other examples of compounds (I) (R^3 being H) and acid addition salts thereof which can be produced from a compound (III) (R^3 being H) and a compound (IV) in a manner similar to that described in Examples 1 to 3 are as follows:

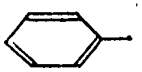
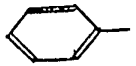
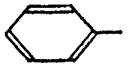
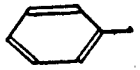
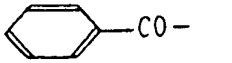
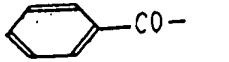
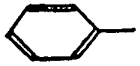
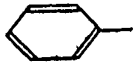
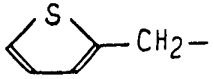
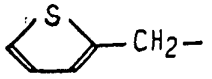
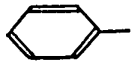
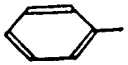
Example	R^4	m	n	X	R^1	R^2	Physical Constant
4	H	1	2	O	H	CH_3—	HCl m.p.: 229°C
5	H	1	2	S	H	H	HBr m.p.: 212—213°C
6	H	1	2	S	H		HBr m.p.: 245°C (decomposition)
7	H	1	2	O			m.p.: 113°C, HBr m.p.: 241°C
8	H	1	2	O	C_2H_5—		oxalate m.p.: 205°C
9	H	1	2	S	CH_3—	CH_3—	HBr m.p.: 251°C
10	H	1	2	O	CH_3—	CH_3—	HBr m.p.: 184—185°C
11	H	1	2	O	CH_3—		acid maleate m.p.: 175°C
12	H	1	2	O	H	H	HCl m.p.: 212°C (decomposition)

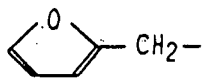
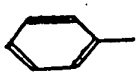
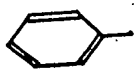
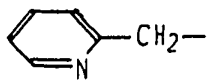
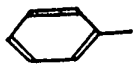
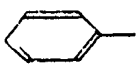
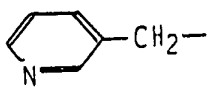
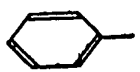
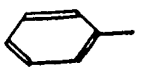
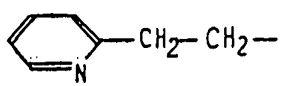
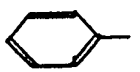
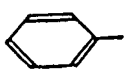
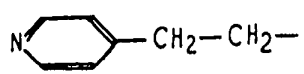
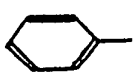
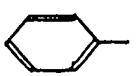
Example	R_4	m	n	X	R^1	R^3	Physical Constant
13	H	1	2	O	H		HCl m.p.: 194—195°C (decomposition)
14	C_2H_5OCO—	1	2	S	H	CH_3—	b.p.: 161—165°C/0.2 mmHg, $n_D^{23.5}$ = 1.5108
15	C_2H_5OCO—	1	2	O	H	H	m.p.: 61—63°C, b.p.:145—148°C/ 0.2 mmHg, n_D^{21} = 1.4819
16	C_2H_5OCO—	1	2	S	H		m.p.: 127°C.
17	C_2H_5OCO—	1	2	O	H		m.p.: 80°C
18	C_2H_5OCO—	1	2	S	CH_3—	CH_3—	b.p.: 145—149/0.15 mmHg, $n_D^{24.5}$ = 1.5028
19	C_2H_5OCO—	1	2	O	C_2H_5—		$n_D^{24.5}$ = 1.5137
20	C_2H_5OCO—	1	2	O			m.p.: 96°C

Example	R^4	m	n	X	R^1	R^2	Physical Constant
21	C_2H_5OCO-	1	2	O	CH_3-	CH_3-	m.p.: 86—87°C
22	C_2H_5OCO-	0	2	S	H	H	b.p.: 148—150°C/0.2 mmHg. $n_D^{22.0} = 1.5190$
23	C_2H_5OCO-	1	2	O	CH_3-		b.p.: 180—183°C/0.25 mmHg, $n_D^{23.5} = 1.5169$
24		1	2	S	H	H	maleate m.p.: 182°C
25		1	2	O	H	CH_3-	HCl m.p.: 250°C
26		1	2	O			HCl m.p.: 236—237°C
27		0	3	O			m.p.: 107°C, oxalate m.p.: 178—179°C

Example	R_4	m	n	X	R^1	R^3	Physical Constant
28		1	2	O	H	H	HCl m.p.: 168°C, maleate m.p.: 154—155°C $n_D^{22.0}$ = 1.5370
29		1	2	O			m.p.: 135°C, maleate m.p.: 180°C.
30		1	2	O			m.p.: 81°C
31		1	2	O			m.p.: 134—135°C
32	CH_3—	1	2	O			m.p.: 135°C, HCl m.p.: 254°C, oxalate m.p.: 245°C
33	CH_3—	1	2	O	H		m.p.: 82—84°C HCl m.p.: 222—223°C

Example	R^4	m	n	X	R^1	R^2	Physical Constant
34	CH_3—	1	2	O	H		m.p.: 54°C, HCl m.p.: 207—208°C, maleate m.p.: 148—149°C
35	CH_3—	1	2	O	CH_3—	CH_3—	HCl m.p.: 228°C, n_D^{24} = 1.5481
36	CH_3—	1	2	O	H	CH_3—	HCl m.p.: 261°C (decomposition), n_D^{23} = 1.4668
37	CH_3—	1	2	O	CH_3—		HCl m.p.: 232 C
38	CH_3—	1	2	S			m.p.: 92—94°C, HCl m.p.: 221°C
39	CH_3—	1	2	O			oxalate m.p.: 174—175 C
40	C_2H_5—	1	2	O			m.p.: 106 C

Example	R^1	m	n	X	R^1	R^3	Physical Constant
41	$CH_3-(CH_2)_3-$	1	2	O			m.p.: 45°C, maleate m.p.: 150—151°C
42	CH_3-CO-	1	2	O			m.p.: 88—89°C
43		1	2	S	H	CH_3-	m.p.: 112—113 C
44		1	2	O			m.p.: 127°C
45		1	2	O	CH_3-	CH_3-	maleate m.p.: 175:°C
46		1	2	O			maleate m.p.: 198°C (decomposition)

Example	R^4	m	n	X	R^1	R^3	Physical Constant
47		1	2	O			maleate m.p.: 175°C (decomposition)
48		1	2	O			m.p.: 104°C. 2HCl m.p.: 232°C (decomposition)
49		1	2	O			2HCl m.p.: 235—236°C (decomposition)
50		1	2	O			m.p.: 134°C, 2HCl m.p.: 205°C
51		1	2	O			m.p.: 108—109°C, 2HCl m.p.: 230°C (decomposition)

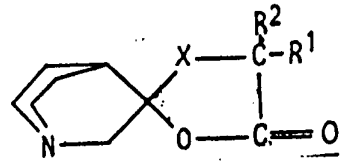
Example 52

A mixture of 9.6 g. of 1-azabicyclo[2.2.2]octan-3-one hydrochloride (3-quinuclidinone hydrochloride), 7.5 g. of 2-hydroxyisobutyric acid and 0.5 g. of concentrated sulphuric acid in 200 ml. of toluene is heated under reflux with stirring in a flask with a water trap attached for 16 hours. After cooling, the reaction mixture is concentrated under reduced pressure, and then 50 ml. of water and 200 ml. of chloroform are added to the residue. The mixture is made alkaline with sodium carbonate. The chloroform layer is separated, washed with water and dried over

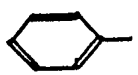
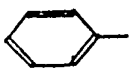
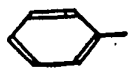
anhydrous magnesium carbonate, and the solvent (chloroform) is distilled off. The dark brown oily residue is column-chromatographed on 160 g. of neutralized, activated alumina and eluted with toluene. The eluate is concentrate to give 1-azabicyclo[2.2.2]-octane-3-spiro-2′-(5′,5′-dimethyl-1′,3′-dioxolan-4′-one) as white crystals melting at 82—85°C. Its maleate melts at 112—114°C.

Example 53 to 56

Other examples of quinuclidine spiro compounds of the formula



and acid addition salts thereof which can be produced from a compound (III) (R^3 and R^4 combinedly representing $—CH_2—CH_2—$, m being 2 and n being 1) and a compound (IV) in a manner similar to that described in Example 52 are as follows:

Example	X	R^1	R^2	Physical Constant
53	O			m.p.: 154—156°C, maleate m.p.: 139—142°C
54	S	H	H	HCl m.p.: 213—214°C
55	O	H		m.p.: 154—155°C
56	S	H	$CH_3—$	HCl m.p.: 234—235°C (decomposition) maleate m.p.: 116—118°C

Example 57

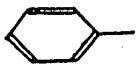
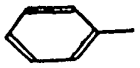
To a mixture of 10.5 g. of 3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane hydrobromide and 10 g. of sodium carbonate in a mixed solvent of 50 ml. of dimethylformamide plus 100 ml. of toluene is added 4.2 g. of benzoyl chloride. The whole mixture is refluxed with stirring for 10 hours. After cooling, insoluble matter is filtered off and the filtrate is concentrated under reduced pressure. The residue is extracted with chloroform, the chloroform layer is washed three times with water and dried over anhydrous magnesium sulphate and then the chloroform is distilled off. The jelly-like residue (pale brown) is dissolved in isopropyl ether and the solution is allowed to stand. The crystals precipitated are collected by filtration and recrystallized from 2-propanol to give 7 g. of 8-benzoyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane as white crystals melting at 127°C.

Example 58

A mixture of 10 g. of 3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane hydrobromide, 10 g. of sodium carbonate and 3.7 g. of allyl bromide in a mixed solvent of 50 ml. of dimethylformamide plus 100 ml. of toluene is refluxed with stirring for 8 hours. After cooling, insoluble matter is filtered off and the filtrate is concentrated under reduced pressure. The residue is extracted with chloroform. The chloroform layer is washed three times with water and dried over anhydrous magnesium sulphate and then the chloroform is distilled off. The jelly-like residue is dissolved in a mixture of ethanol and isopropyl ether and ethanolic hydrochloric acid is added to the solution. The crystals formed are collected by filtration and recrystallized from 2-propanol to give 6.5 g. of 8-allyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride as white crystals melting at 244°C (decomposition).

Example 59

Proceeding by the method of Examples 57 and 58, but substituting equivalent amounts of appropriate starting materials, the following compound may be produced.

Example	R^4	n	m	X	R^1	R^2	R^3	Physical Constant
59	$CH\equiv C-CH_2-$	1	2	O			H	oxalate m.p.: 159—161 C

Compounds identical to the products of above Examples 1, 2, 14—21, 23—26, 28—32, 34—37 and 40—51, may likewise be prepared.

Example 60

To a mixture of 25 ml. of 37 % formaldehyde and 25 g. of 90 % formic acid is added 10 g. of 3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane. The mixture is refluxed with stirring for 5 hours. After cooling, the reaction mixture is made acid with 120 ml. of 4N hydrochloric acid and concentrated under reduced pressure. The crystals obtained are recrystallized twice from ethanol to give 5 g. of 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride as white crystals melting at 254°C.

Proceeding by the method of Example 60, but substituting equivalent amounts of appropriate starting materials, the compounds identical to the products of above Examples 34—37 may also be produced.

Example 61

A mixture of 19 g. of 8-ethoxycarbonyl-3-methyl-2-oxo-1-oxa-4-thia-8-azaspiro-[4.5]decane and 200 ml. of a 20 % solution of hydrogen bromide in acetic acid is heated on a water bath for 3 hours. After cooling, the acetic acid is distilled off under reduced pressure. The brown solid residue is crystallized from 2-propanol and recrystallized from methanol to give 10 g. of 3-methyl-2-oxo-1-oxa-4-thia-8-azaspiro-[4.5]decane hydrobromide as white crystals melting at 227°C.

Example 62

A mixture of 20 g. of 8-ethoxycarbonyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro-[4.5]decane, 35 g. of potassium hydroxide, 300 ml. of methanol and 50 ml. of water is heated on a water bath for 22 hours. After cooling, the solvent is distilled off and water is added to the residue. The oil separated is extracted with chloroform. The chloroform layer is washed with water and dried over anhydrous magnesium sulphate and then the chloroform is distilled off to give 11 g. of 3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane as white crystals melting at 113°C.

Proceeding by the method of Examples 61 and 62, but substituting equivalent amounts of appropriate starting materials, compounds identical to the products of above Examples 5, 6, 8, 9 and 10 may also be produced.

Example 63

To a solution of 10 g. of 8-benzyl-3-methyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]-decane hydrochloride in 30 ml. of water are added 50 ml. of ethanol and 5 g. of 10% palladium-carbon. Reduction is carried out with stirring under normal pressure at room temperature until the absorption of hydrogen stops. After the reduction, the palladium-carbon is filtered off, and the filtrate is concentrated under reduced pressure. The white crystals obtained are recrystallized twice from ethanol to give 4.5 g. of 3-methyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane hydrochloride as white crystals melting at 229°C.

Example 64

To a solution of 10 g. of 8-benzyl-2-oxo-3-phenyl-1,4-dioxa-8-azaspiro[4.5]-decane hydrochloride in 70 ml. of water are added 100 ml. of 2-propanol and 6 g. of 5% palladium-carbon. The resulting mixture is placed in an autoclave, the autoclave is charged with hydrogen at 80 atmospheres, and then the reduction is carried out at 60°C for 1 hour. After cooling, the palladium-carbon is filtered off, and the filtrate is concentrated under reduced pressure. The white crystals obtained are washed with 2-propanol and recrystallized from ethanol to give 5 g. of 2-oxo-3-phenyl-1,4-dioxa-8-azaspiro[4.5]decane as white crystals melting at 194—195°C.

Proceeding by the method of Examples 63 and 64, but substituting equivalent amounts of appropriate starting materials, the compounds identical to the products of above Examples 7 and 12 may be obtained.

Example 65

To a solution of 8 g. of 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]-decane (produced by Example 32) in a mixed solvent of 80 ml. of chloroform plus 30 ml. of methanol is added 5 g. of methyl iodide. The mixture is heated under reflux with stirring for 2.5 hours, and then further heated for 2.5 hours to complete the reaction. After cooling, the crystals obtained are collected by filtration and recrystallized from methanol to give 8 g. of 8,8-dimethyl-3,3-diphenyl-2-oxo-1,4-dioxa-

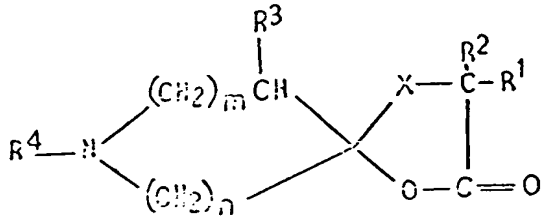
8-azaspiro[4.5]decanium iodide as white crystals melting at 266—267°C (decomposition).

Other quaternary ammonium salts which can be produced from a compound (I) and alkyl halide or dimethyl sulphate by the method of Example 65 are as follows:

Compound	Quaternizing Agent	Melting Point of Quaternary Salt (decomposition)
Example 26	methyl iodide	214°C
Example 27	methyl iodide	185—186°C
Example 28	methyl iodide	233°C
Example 30	methyl iodide	216°C
Example 32	dimethyl sulfate	168°C
	methyl hydrogensulfate	241°C
	ethyl bromide	249°C
Example 33	methyl iodide	226°C
Example 34	methyl iodide	249°C
Example 35	methyl iodide	236°3C
Example 36	methyl iodide	248°C
Example 37	methyl iodide	229°C
Example 38	methyl iodide	268°C
Example 39	methyl iodide	214—216°C
Example 41	methyl iodide	231°C
Example 46	methyl iodide	196—197°C
Example 48	methyl iodide	211°C
Example 51	methyl iodide (2 moles)	206°C
Example 52	methyl iodide	236—238°C
Example 53	methyl iodide	255—257°C
Example 54	methyl iodide	219—221°C.
Example 55	methyl iodide	228—230°C
Example 56	methyl iodide	233—234°C
Example 58	methyl iodide	183—185°C
Example 59	methyl iodide	196°C

WHAT WE CLAIM IS:—

1. A compound of the general formula:

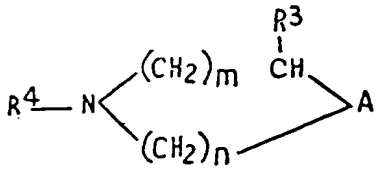


(I)

or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof, wherein R^1 and R^2 are the same or different and are H, CH_3, C_2H_5, phenyl, *p*-chlorophenyl or benzyl; X is O or S, R^3 is H and R^4 is H, alkyl having 1 to 4 carbon atoms, methoxycarbonyl, ethoxycarbonyl, acetyl, benzoyl, benzyl, phenethyl, pyridylmethyl, pyridylethyl, furfuryl, thenyl, cinnamyl, cinnamoyl, allyl or propargyl, and m plus n is 2 or 3, m being 0 or 1 and n being 2 or 3; or R^3 and R^1 together represent $—CH_2—CH_2—$ and m is 2 and n is 1.

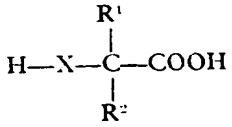
2. 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
3. 8-butyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
4. 8-methyl-3-methyl-3-phenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
5. 8-methyl-3-benzyl-3-phenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
6. 8-(2-thenyl)-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
7. 8-methyl-3,3-diphenyl-2-oxo-1-oxa-4-thia-8-azaspiro[4.5]decane.
8. 8-cinnamyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane.
9. 1-azabicyclo-[2.2.2]octane-3-spiro-2′-(5′,5′-diphenyl-1′,3′-dioxolan-4′-one).
10. 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane methoiodide.
11. 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane ethobromide.
12. 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane methyl hydrogensulphate.
13. 8-methyl-3,3-diphenyl-2-oxo-1,4-dioxa-8-azaspiro[4.5]decane dimethyl sulphate.

14. A method of producing a compound as claimed in Claim 1, which comprises reacting a compound having the general formula:



(III)

with a compound having the formula:



(IV)

wherein A is —CO— or —C(OH)$_2$—, and R^1, R^2, R^3, R^4, X, m and n are as defined in Claim 1.

15. A compound as claimed in Claim 1, substantially as hereinbefore described with reference to any of the foregoing Examples.

16. A method for producing a compound as claimed in Claim 1, substantially as hereinbefore described with reference to any of the Examples.

17. A compound as claimed in Claim 1, when prepared by a method as claimed in Claims 14 or 16.

18. A pharmaceutical solution for administration by injection, which comprises a compound as claimed in any of claims 1 to 13, 15 or 17 dissolved in a physiologically-acceptable liquid.